PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/13, 9/12

A1

(11) International Publication Number: **WO 98/01147**

(43) International Publication Date: 15 January 1998 (15.01.98)

(21) International Application Number: PCT/GB97/01851

(22) International Filing Date: 7 July 1997 (07.07.97)

(30) Priority Data:

9614326.8	8 July 1996 (08.07.96)	GB
60/023,048	2 August 1996 (02.08.96)	US

(71) Applicant *(for all designated States except US)*: RHONE-POULENC RORER LIMITED [GB/GB]; RPR House, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4TA (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: BELL, Alexander [GB/GB]; Rhone-Poulenc Rorer Limited, London Road, Holmes Chapel, Cheshire CW4 8BE (GB).

(74) Agent: CAFFIN, Lee; Rhone-Poulenc Rorer Limited, Patent Dept., Rainham Road South, Dagenham, Essex RM10 7XS (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MEDICINAL CYCLOSPORIN-A AEROSOL SOLUTION FORMULATION

(57) Abstract

The invention is related to a solution formulation of Cyclosporin A in 1,1,1,2,3,3,3-heptafluoropropane which is suitable for administration to a patient by inhalation using any standard medicinal aerosol device. Standard excipients normally used in medicinal aerosol formulations to aid valve lubrication or improve flavour may also be added. Other medicaments in solution or suspension may be used in addition to Cyclosporin A and other propellants in addition to 1,1,1,2,3,3,3-heptafluoropropane may be used.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

MEDICINAL CYCLOSPORIN-A AEROSOL SOLUTION FORMULATION

This invention relates to the administration of Cyclosporin A by inhalation via a solution aerosol formulation. Such administrations will have particular benefits in the treatment of asthma or other respiratory diseases but are also expected to provide a convenient method of administering the drug for other purposes such as immunosuppression, treatment of auto-immune diseases, antiparasitic treatments, etc.

Cyclosporin A was developed as an immunosuppressant but has more recently been proposed as a treatment for asthma and other respiratory diseases. EP-A1-0504761 deals with the use of Cyclosporin A in pulmonary delivery systems for this purpose, and is primarily concerned with the administration via inhalation of a particular crystalline form of Cyclosporin A designated CY-A X-III. The use of Cyclosporin A as a solution in chlorofluorocarbon propellants in aerosol inhalation systems is also described. This is not a preferred option however, it being stated that the administration of Cyclosporin A in solution will have none of the advantages of administration of CY-A X-III.

WO 95/24892 describes the use of tocopherol and derivatives as surfactants to stabilise suspensions of a number of medicaments in hydrofluorocarbon

propellants such as HFC 134a (1,1,1,2-tetrafluoroethane) and HFC 227 (1,1,1,2,3,3,3-heptafluoropropane). Among the formulations exemplified and claimed is a suspension of Cyclosporin A in HFC 134a with tocopherol as suspension aid. WO 96/06598 describes the use of polyglycolised glycerides in similar formulations and also exemplifies suspensions of Cyclosporin A in HFC 134a.

We have now surprisingly found that it is possible to dissolve Cyclosporin A in a particular hydrofluorocarbon, namely propellant HFC 227 in concentrations sufficient to provide a composition suitable for charging to a medicinal aerosol device to provide therapeutic doses of Cyclosporin A by inhalation. This is particularly surprising since Cyclosporin A is sufficiently insoluble in the related hydrofluorocarbon, HFC 134a, to be used in a suspension rather than a solution formulation.

Thus, according to one aspect of the present invention there is provided a pharmaceutical solution aerosol formulation comprising Cyclosporin A in 1,1,1,2,3,3,3-heptafluoropropane (HFC 227).

The solubility of Cyclosporin A in HFC 227 is such that no co-solvent is required, although excipients may be added for other principal purposes, such as to improve valve function.

Excipients conventionally used in pharmaceutical aerosol formulations may be added if required, in particular excipients to improve valve lubrication and/or excipients to modify flavour. Particular lubricants that may be mentioned include ethanol and polyethoxylated compounds, especially polyethylene glycol. Either 96% or absolute ethanol may conveniently be used. Where used, polyethylene glycol with a mean molecular weight between 200 to 3000, preferably between 400 to 2000, e.g. 1500, is preferred. Examples of other polyethoxylated compounds that may be used as lubricants include polysorbates, e.g. Polysorbate 80, and alkyl aryl polyether alcohols. e.g. tyloxapol. Examples of other lubricating excipients that may be mentioned include high molecular weight fully halogenated chlorofluorocarbons and esters of medium chain fatty acids, lecithins, oleic acid or sorbitan esters. The concentration of lubricant will depend on the type of lubricant and the nature of the valve. Ethanol addition will normally be less than 10%v/v, preferably between 2% to 7% v/v (eg about 5%v/v). The concentration of other lubricants will typically fall within the range of about 0.01 to 4%v/v, more typically about 0.1 to 2%v/v. If necessary a small amount of polar liquid, including ethanol, may be added as adjuvant to help dissolve such lubricants.

Flavour modifying excipients that may be added include peppermint oil, menthol, Dentomint (Dentomint is a trade name), saccharin, saccharin sodium and aspartame. A solid excipient, preferably milled to a low particle size to reduce settling, may be used. The concentration of flavouring excipient will typically be 0.005 to 4%v/v, more typically 0.01 to 1%v/v.

Preferably the concentration of Cyclosporin A in the solution will be in the range 1 to 400mg/ml, more preferably in the range 5 to 100mg/ml and most preferably in the range of about 10 to 50mg/ml. Thus, Cyclosporin A may preferably constitute up to about 5% weight per total volume of solution.

Whilst it is envisaged that HFC 227 will generally be used as sole propellant, formulations also comprising one or more different propellants are also included within the scope of the invention, provided that there is sufficient HFC 227 present to maintain a stable solution at the concentration required to deliver an effective dose of the medicament. Preferably the alternative propellant or propellants will not be chlorocarbons or chlorofluorocarbons. Examples of other propellants which may be used include HFC 134a, HFC 152, low molecular weight hydrocarbons and dimethyl ether.

Formulations containing one or more additional medicaments are also considered to be within the scope of the invention. The additional medicaments may also be in solution or they may be in the form of a suspension of fine drug particles in the conventional manner. In this latter case surfactants or adjuvants commonly used to stabilise such suspensions may be present.

Formulations according to the invention may be used to manufacture pharmaceutical aerosols for treatment of respiratory diseases, in particular respiratory obstructive airways diseases (ROAD) such as asthma. Thus, according to another aspect of the invention there is provided the use of Cyclosporin A for the manufacture of a solution aerosol formulation in 1,1,1,2,3,3,3-heptafluoropropane for the treatment of respiratory diseases, in particular respiratory obstructive airways diseases such as asthma.

A further aspect of the invention provides a method of treating respiratory diseases, including ROAD, comprising administering by inhalation a spray or aerosol derived from a formulation comprising Cyclosporin A dissolved in 1,1,1,2,3,3,3-heptafluoropropane.

According to yet another aspect of the invention there is provided a pharmaceutical aerosol device

containing a formulation comprising Cyclosporin A dissolved in 1,1,1,2,3,3,3-heptafluoropropane.

It is envisaged that the formulation according to the invention will be used in a standard metered dose aerosol inhaler device (MDI). Such devices typically use a 50µl or 100µl valve. A typical dose of Cyclosporin A for inhalation is expected to be approximately 25mg per day, delivered in individual doses of 1 to 10mg per inhalation, preferably 1 to 5mg per inhalation. This will require a solution concentration of Cyclosporin A of about 10 to 100mg/ml. It will be appreciated that different doses may be required depending on the disease to be treated, and solution concentration and/or valve size can be varied accordingly.

MDI devices commonly use a spacer to increase the path length between spray orifice and the mouth of the patient. This slows down the aerosol jet and allows larger aerosol particles to settle out before entering the patient's mouth. Whilst not essential to the operation of the present invention the use of a spacer has been found to reduce the incidence of larger particles with minimum effect on respirable fraction.

The formulations according to the invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Canisters

generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated, and closed with a metering valve. The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France, Bespak plc. UK and 3M-Neotechnic Ltd, UK.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminium can to form an empty canister. The drug solution is then filled via a filling machine through the metering valve into the canister. Alternatively a solution of Cyclosporin A in ethanol, at a concentration appropriate to give the correct concentrations of each component in the

final formulation, can be added to an aluminium can and a metering valve crimped in place to form a canister. The required amount of propellant can then be added through the valve.

Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler for administration to the medicament into the lungs or nasal cavity of a patient. Suitable channelling devices comprise for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. Typically each filled canister for use in a metered dose inhaler contains 100 to 250 metered doses or puffs of medicament.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated that the precise dose administered will depend on the age and condition of the patient and the frequency of administration and will ultimately be at the discretion of the attendant physician. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1, 2, 3 or 4 puffs each time.

The filled canisters and metered dose inhalers described herein comprise further aspects of the present invention.

EXAMPLE 1

The solubility of Cyclosporin A in a number of aerosol propellants was determined as follows:

A small quantity of Cyclosporin A was weighed into a plastic-coated glass bottle and a continuous flow valve crimped onto the bottle. Propellant was added to the bottle from an aerosol can using a suitable transfer valve. The quantity added was chosen to leave some undissolved Cyclosporin A and therefore ensure a saturated solution. The suspension was left to equilibrate overnight at 20°C and filtered through a 0.5μm polytetrafluoroethylene (PTFE) membrane using a pressure filtration apparatus into an empty crimped receptor bottle to give a clear saturated solution. The weight of solution in the bottle was determined and the propellant was then carefully vented off to leave the Cyclosporin A. This was dissolved in a measured volume of ethanol and the concentration of the solution measured using High Pressure Liquid Chromatography (HPLC) in order to give the quantity of Cyclosporin A in the original propellant solution.

The above technique was found not to be suitable for determining the solubility of Cyclosporin A in HFC 227 since Cyclosporin A appears to dissolve in less

than its own weight of HFC 227. An approximate solubility was determined by adding a weighed quantity of Cyclosporin A to a plastic-coated glass bottle and crimping a continuous flow valve onto the bottle. Excess HFC 227 was added to dissolve all the Cyclosporin A. Propellant was then vented off and the bottle reweighed in stages. An attempt was made to observe the first appearance of precipitated Cyclosporin A. However the solutions were extremely viscous and contained numerous small bubbles. It was therefore only possible to obtain an approximate solubility.

The following results were obtained:

Propellant	Solubility (mg/ml)
CFC 11	ca. 28
CFC 12	0.13
CFC 114	0.55
CFC 113	30
HFC 134a	ca. 3 - 5
HFC 227	>400

EXAMPLE 2

500mg of Cyclosporin A was weighed into a plastic-coated glass bottle. 10ml of HFC 227 was added and a 100µl metering valve immediately crimped into place. The resulting aerosol delivered 5mg Cyclosporin A per actuation. The solution was stable over a period of three months.

EXAMPLE 3

A number of formulations containing ethanol were prepared. The ethanol was added to act as lubricant for the aerosol valve and improve dose reproducibility. An ethanolic solution of Cyclosporin A was produced at a concentration suitable for producing the required final concentration in the aerosol. A measured quantity was added to a standard aluminium aerosol can and a metering valve crimped on top. The required amount of propellant was added to the can through the valve. All solutions were found to be stable to chemical degradation on storage at 45°C for one month and to precipitation at temperatures as low as -78°C.

A number of HFC 227 formulations were subjected to the standard Anderson Impactor test for respirable fraction with the following results:

Formulation	1	2	3	4	5
Cyclosporin A (mg/ml)	50	50	25	25	10
Ethanol (%v/v)	5	5	5	5	5
HFC 227 (%v/v)	95	95	95	95	95
Valve volume (µl)	50	100	50	100	50
Respirable fraction (%)	33	29	55	53	72

EXAMPLE 4

A number of formulations containing a mixture of propellants HFC 227 and HFC 134a were prepared. Ethanol was added as appropriate. The required amount of Cyclosporin A was weighed into a 2 ounce plastic-coated glass bottle and the required amount of ethanol added, if required. A standard 50μL metering valve was clamped in place and the required weight of each propellant added through the valve. The bottle was shaken until the Cyclosporin A was fully dissolved. The formulations were subjected to the standard Anderson Impactor test for respirable fraction with the following results:

Formulation	1	2	3	4
Cyclosporin A (mg/ml)	50	50	50	50
HFC 227 (%v/v)	51.2	41.2	28.5	17.3
HFC 134a (%v/v)	48.8	57.5	69.0	78.9
Ethanol (%v/v)	0	1.3	2.5	3.8
Valve volume (μL)	50	50	50	50
Respirable fraction (%)	27	30	31	32

CLAIMS

1) A pharmaceutical aerosol solution formulation comprising Cyclosporin A in 1,1,1,2,3,3,3-heptafluoropropane.

2) A pharmaceutical aerosol solution formulation according to claim 1 further comprising an excipient to aid valve lubrication.

3) A pharmaceutical aerosol solution formulation according to claim 2 wherein the excipient to aid valve lubrication comprises ethanol.

4) A pharmaceutical aerosol solution formulation according to claim 3 wherein the concentration of ethanol in the solution is less than 10%v/v.

5) A pharmaceutical aerosol solution formulation according to any one of claims 2 to 4 wherein the concentration of ethanol in the solution is about 5%v/v.

6) A pharmaceutical aerosol solution formulation according to claim 2 wherein the excipient to aid valve lubrication is selected from polyethoxylated compounds, high molecular weight fully halogenated chlorofluorocarbons, esters of medium chain fatty acids, lecithins, oleic acid or sorbitan esters.

7) A pharmaceutical aerosol solution formulation according to claim 6 wherein the concentration of lubricating excipient in the solution is between 0.01 to 4% v/v.

8) A pharmaceutical aerosol solution formulation according to claim 6 wherein the concentration of lubricating excipient in the solution is between 0.1 to 2% v/v.

9) A pharmaceutical aerosol solution formulation according to any one of claims 6 to 8 wherein the lubricating excipient comprises polyethylene glycol (PEG) with a mean molecular weight between 200 and 3000 units.

10) A pharmaceutical aerosol solution formulation according to any one of claims 6 to 8 wherein the lubricating excipient comprises PEG 1500.

11) A pharmaceutical aerosol solution formulation according to any of claims 6 to 10 further containing an adjuvant to solubilise the lubricating excipient.

12) A pharmaceutical aerosol solution formulation according to claim 11 wherein the adjuvant is ethanol.

13) A pharmaceutical aerosol solution formulation according to any preceding claim further containing a flavour modifying excipient.

14) A pharmaceutical aerosol solution formulation according to any preceding claim wherein the concentration of Cyclosporin A in solution is between 1 to 400mg/ml.

15) A pharmaceutical aerosol solution formulation according to any preceding claim wherein the concentration of Cyclosporin A in solution is between 5 to 100mg/ml.

16) A pharmaceutical aerosol solution formulation according to any preceding claim wherein the concentration of Cyclosporin A in solution is between 10 to 50mg/ml.

17) A pharmaceutical aerosol solution formulation according to any preceding claim further containing an alternative propellant or mixture of alternative propellants.

18) A pharmaceutical aerosol solution formulation according to claim 17 wherein the alternative propellant is 1,1,1,2-tetrafluoroethane.

19) A pharmaceutical aerosol solution formulation according to any one of claims 1 to 16 wherein the

propellant consists essentially of 1,1,1,2,3,3,3-heptafluoropropane.

20) A pharmaceutical aerosol solution formulation according to any preceding claim further containing one or more extra medicaments.

21) The use of Cyclosporin A to produce an aerosol solution formulation according to any preceding claim for the treatment of respiratory diseases.

22) A method of treating respiratory diseases comprising administering by inhalation a spray or aerosol derived from a formulation according to any one of claims 1 to 20.

23) A pharmaceutical aerosol device containing an aerosol solution formulation according to any one of claims 1 to 20.

24) A pharmaceutical aerosol solution formulation as substantially described herein with reference to the Examples.

INTERNATIONAL SEARCH REPORT

Int .onal Application No
PCT/GB 97/01851

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/13 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 06598 A (ABBOTT LAB) 7 March 1996 cited in the application	1-3,6, 11-16, 21-23
Y	see page 1, line 20-22 see page 4, line 29-20 see page 5, line 32; claims 3,9,13-15; examples 5,6; tables 2,3 see page 1, line 32-35	1-3,6, 11-19, 21-23

X	WO 95 24892 A (ABBOTT LAB) 21 September 1995 cited in the application see page 2, line 11-14 see page 1, line 32-36; claims 1-3,7-9,11,12,14	1-3,6, 11,12, 14-16, 21-23

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
22 September 1997	13. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kanbier, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 97/01851

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 633 019 A (ASTA MEDICA AG) 11 January 1995	1-4,6, 11-13, 17-23
A	see page 8, line 23-32 see page 8, line 56 see page 9, line 1 see page 9, line 13-17; claims 20-24; examples 1-3	14-16
Y	WO 96 11943 A (ASTRA AB) 25 April 1996	1-3,6, 11-19, 21-23
	see page 1, line 15 see page 28, line 30 - page 29, line 19	
Y	EP 0 504 760 A (SANDOZ LTD.) 23 September 1992	1-3,6, 11-19, 21-23
	see page 10, line 26-55; claims 21,22; example 7 see page 2, line 4	

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 97/01851

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606598 A	07-03-96	US 5635159 A	03-06-97
		AU 3329295 A	22-03-96
		CA 2195874 A	07-03-96
		EP 0777467 A	11-06-97
WO 9524892 A	21-09-95	AU 1980495 A	03-10-95
EP 0633019 A	11-01-95	DE 4322703 A	12-01-95
		JP 7070557 A	14-03-95
		US 5536444 A	16-07-96
WO 9611943 A	25-04-96	AU 3713395 A	06-05-96
		EP 0783519 A	16-07-97
		FI 971499 A	10-06-97
		NO 971625 A	30-05-97
		PL 319631 A	18-08-97
EP 0504760 A	23-09-92	AU 658172 B	06-04-95
		AU 1294092 A	24-09-92
		CA 2063106 A	19-09-92
		CH 685229 A	15-05-95
		CS 9200785 A	14-10-92
		DE 4208258 A	24-09-92
		ES 2093130 T	16-12-96
		FR 2674249 A	25-09-92
		GB 2253853 A,B	23-09-92
		IE 67627 B	17-04-96
		IL 101244 A	31-10-96
		IT 1255040 B	13-10-95
		JP 2549794 B	30-10-96
		JP 5085940 A	06-04-93
		LU 88087 A	27-10-93
		NZ 241975 A	27-04-94
		ZA 9201987 A	20-09-93